



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB99/00800 (22) International Filing Date: 16 March 1999 (16.03.99) (30) Priority Data: 9805559.3 16 March 1998 (16.03.98) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): DAWSON, Gerard, Raphael [GB/GB]; Terlings Parks, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: HORGAN, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: COMBINATION OF A GABA-A ALPHA 5 INVERSE AGONIST AND A NICOTINIC AGONIST (57) Abstract The present invention relates to a combination of a nicotinic agonist and an inverse agonist of the GABA _A α_5 receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.		

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COMBINATION OF A GABA-A ALPHA 5 INVERSE AGONIST AND
A NICOTINIC AGONIST

5 The present invention relates to a combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.

10 Alzheimer's Disease is a poorly understood neurodegenerative condition mainly affecting the elderly but also younger people who are generally genetically predispositioned to it.

One postulated method of treatment comprises the administration of nicotinic agonists which act on the cholinergic system. However this method suffers from the disadvantages that these compounds induce a range of side-effects including diarrhoea, salivation and nausea.

15 The present invention provides a new and surprisingly effective synergistic combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype for separate, sequential or simultaneous administration.

20 The present invention provides a greater than expected improvement in the condition of subjects suffering from a neurodegenerative with an associated cognitive deficit, such as Alzheimer's Disease or Parkinson's disease, or from a cognitive deficit which may arise from a normal process such as aging or from an abnormal process such as injury, than would be expected from administration of the active ingredients alone. Further, the combination allows for a lower overall dose of each of the active ingredients to be administered thus reducing side effects and decreasing any reduction in the effectiveness of each of the active ingredients over time.

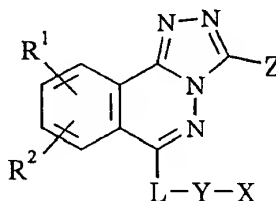
25 Nicotinic agonists which may be used include any which are known to the skilled person. Examples are nicotine, lobeline, tetramethylammonium, 1,1-dimethyl-4-phenylpyrazinium and ABT 418.

Any inverse agonist of the GABA_A α_5 receptor subtype may be used which fulfills the criteria of WO-A-9625948. The inverse agonist may be either binding selective for the α_5 subtype or functionally selective, or both. Thus the inverse agonist is preferably an antagonist, or has
5 insignificant agonist or inverse agonist properties at the other GABA_A α receptor subtypes when measured in oocytes as described in WO-A-9625948.

Thus the inverse agonist preferably has a functional efficacy at the α_5 receptor subunit of less than -20% and functional efficacies at the α_1 ,
10 α_2 , and α_3 receptor subunits of between -20 and +20%. By functional efficacy is meant the percentage modulation of the EC₂₀ response produced by GABA, upon coadministration of the inverse agonist, in oocytes expressing GABA_A receptor channels containing the α receptor subunit under test. Details of this measurement are given in WO-A-9625948.

15 The inverse agonist preferably binds selectively to GABA_A receptors containing the α_5 subunit 10, 25 and particularly 50 times compared to GABA_A receptors subunits containing the α_1 , α_2 or α_3 subunits. Preferably this binding selectivity is shown over all these subunits.

A preferred class of inverse agonists, which are disclosed in
20 WO-A-9850385, are of formula I:



wherein:

25 R¹ is hydrogen, halogen or CN or a group C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₂₋₄alkenyloxy or C₂₋₄alkynyloxy, each of which groups is unsubstituted or substituted with one or two halogen atoms or

with a pyridyl or phenyl ring each of which rings may be unsubstituted or independently substituted by one or two halogen atoms or nitro, cyano, amino, methyl or CF₃ groups;

R² is hydrogen, halogen or CN or a group C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₂₋₄alkenyloxy or C₂₋₄alkynyloxy each of which groups is unsubstituted or substituted with one or two halogen atoms;

L is O, S or NRⁿ where Rⁿ is H, C₁₋₆alkyl or C₃₋₆cycloalkyl;

X is a 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur, or a 6-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms, the 5- or 6-membered heteroaromatic ring being optionally fused to a benzene ring and the heteroaromatic ring being optionally substituted by R^x and/or R^y and/or R^z, where R^x is halogen, R³, OR³, OCOR³, NR⁴R⁵, NR⁴COR⁵, tri(C₁₋₆alkyl)silylC₁₋₆alkoxyC₁₋₄alkyl, CN or R⁹, R^y is halogen, R³, OR³, OCOR³, NR⁴R⁵, NR⁴COR⁵ or CN and R^z is R³, OR³ or OCOR³, where R³ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, hydroxyC₁₋₆alkyl and R³ is optionally mono, di- or tri-fluorinated, R⁴ and R⁵ are each independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl or CF₃ or R⁴ and R⁵, together with the nitrogen atom to which they are attached, form a 4-7 membered heteroaliphatic ring containing the nitrogen atom as the sole heteroatom, and R⁹ is benzyl or an aromatic ring containing either 6 atoms, 1, 2 or 3 of which are optionally nitrogen, or 5 atoms, 1, 2 or 3 of which are independently chosen from oxygen, nitrogen and sulphur, at most one of the atoms being oxygen or sulphur, and R⁹ is optionally substituted by one, two or three substituents independently chosen from halogen atoms and C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₂₋₄alkenyloxy and C₂₋₄alkynyloxy groups each of which groups is unsubstituted or substituted by one, two or three halogen atoms, and when X is a pyridine derivative, the pyridine derivative is optionally in the form of the N-oxide and providing that when X is a tetrazole derivative it

is protected by a C₁₋₄alkyl group; or X is phenyl optionally substituted by one, two or three groups independently selected from halogen, cyano, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and C₃₋₆cycloalkyl;

Y is optionally branched C₁₋₄alkylidene optionally substituted by an
5 oxo group or Y is a group (CH₂)_jO wherein the oxygen atom is nearest the group X and j is 2, 3 or 4;

Z is a 5-membered heteroaromatic ring containing 1, 2 or 3
heteroatoms independently selected from oxygen, nitrogen and sulphur, at
most one of the heteroatoms being oxygen or sulphur and providing that
10 when two of the heteroatoms are nitrogen an oxygen or sulphur atom is also present and that when one of the atoms is oxygen or sulphur then at least one nitrogen atom is present, or a 6-membered heteroaromatic ring containing 2 or 3 nitrogen atoms, Z being optionally substituted by R^v and/or R^w, where R^v is halogen, R⁶, NR⁷R⁸, NR⁷COR⁸, CN, furyl, thienyl,
15 phenyl, benzyl, pyridyl or a 5-membered heteroaromatic ring containing at least one nitrogen atom and optionally 1, 2 or 3 other heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the other heteroatoms being oxygen or sulphur and R^w is R⁶ or CN;

R⁶ is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl,
20 hydroxyC₁₋₆alkyl, C₁₋₆alkoxy, C₂₋₆alkenyloxy, C₂₋₆alkynyloxy, CH₂F or CF₃; and

R⁷ and R⁸ are each independently hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl or CF₃ or R⁷ and R⁸, together with the nitrogen atom to which they are attached, form a 4-7 membered heteroaliphatic
25 ring containing the nitrogen atom as the sole heteroatom;

or a pharmaceutically acceptable salt thereof.

As used herein, the expression "C₁₋₆alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and
30 t-butyl. Derived expressions such as "C₁₋₄alkyl", "C₂₋₄alkenyl",

"C₂₋₆alkenyl", "hydroxyC₁₋₆alkyl", "C₂₋₄alkyl" and "C₂₋₆alkynyl" are to be construed in an analogous manner.

The expression "C₃₋₆cycloalkyl" as used herein includes cyclic propyl, butyl, pentyl and hexyl groups such as cyclopropyl and cyclohexyl.

5 Suitable 5- and 6-membered heteroaromatic rings include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl and thiadiazolyl groups. A suitable 5-membered heteroaromatic ring containing four nitrogen atoms is tetrazolyl. Suitable 6-membered heteroaromatic rings
10 containing three nitrogen atoms include 1,2,4-triazine and 1,3,5-triazine.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

As used herein the term "C₁₋₆alkoxy" includes methoxy and ethoxy groups, and straight-chained, branched and cyclic propoxy, butoxy,
15 pentoxy and hexoxy groups, including cyclopropylmethoxy. Derived expressions such as "C₂₋₆alkenyloxy", "C₂₋₆alkynyloxy", "C₁₋₄alkoxy", "C₂₋₄alkenyloxy" and "C₂₋₄alkyloxy" should be construed in an analogous manner.

Four particular compounds which can be used are:

20 6-(1-methylimidazol-4-yl)methyloxy-3-(5-methylisoxazol-3-yl)-1,2,4-triazolo[3,4-a]phthalazine;
3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methyloxy-1,2,4-triazolo[3,4-a]phthalazine;
3-(5-methylisoxazol-3-yl)-6-(2-pyridyl)-1,2,4-triazolo[3,4-a]phthalazine;
25 and
3-(5-methylisoxazol-3-yl)-6-(1-methylimidazol-4-yl)-1,2,4-triazol-3-ylmethyloxy-1,2,4-triazolo[3,4-a]phthalazine.

The second of the above compounds is particularly favoured.

The present invention also provides a pharmaceutical composition
30 comprising an nicotinic agonist, an inverse agonist of the GABA_A α₅ receptor subtype and a pharmaceutically acceptable carrier.

There is also provided a kit of parts comprising a first pharmaceutical composition comprising an nicotinic agonist and a first pharmaceutically acceptable carrier and a second pharmaceutical composition comprising an inverse agonist of the GABA_A α_5 receptor subtype and a second pharmaceutically acceptable carrier for simultaneous, sequential or separate administration.

There is further provided a combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype for use in a method of treatment of the human body, particularly for the treatment of a neurodegenerative disorder with associated cognitive deficit such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising from a normal process such as aging or of an abnormal process such as injury. The combination is particularly beneficial in the treatment of Alzheimer's Disease.

There is also provided the use of a combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype in the manufacture of a medicament for the treatment of a neurodegenerative disorder such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising from a normal process such as aging or of an abnormal process such as injury. The treatment of Alzheimer's Disease is particularly preferred.

There is also disclosed a method of treatment of a subject suffering from a neurodegenerative disorder, such as Alzheimer's Disease or Parkinson's disease, or a cognitive deficit arising from a normal process such as aging or an abnormal process such as injury, which comprises administering to that subject a therapeutically effective amount of a combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype. The treatment of Alzheimer's Disease is particularly preferred.

The pharmaceutical compositions of the present invention are preferably in unit dosage forms such as tablets, pills, capsules, powders,

granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For

5 preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or

10 surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When

referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the

15 composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of each active ingredient of the present invention. Typical unit dosage forms

20 contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of each active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can

comprise an inner dosage and an outer dosage component, the latter being

25 in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of

30 polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed
5 oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

10 For the treatment of a neurodegenerative condition, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day of each active ingredient. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside
15 these limits may be used.

The synergistic effect of the combination of the present invention can be shown, for example, by comparing the combined dosage of the combination with dosages of the same amount of each of the active ingredients separately on subjects using the Mini-Mental State
20 Examination (MMSE) as described in Folstein and Folstein J. Psychiat. Res., 1975, 12, 189-198 or a variant thereof as discussed in Tombaugh and McIntyre, JAGS, 1992, 40, 922-935.

CLAIMS

1. A combination of an nicotinic agonist and an inverse agonist of the
GABA_A α_5 receptor subtype for separate, sequential or simultaneous
5 administration.
2. A combination according to claim 1 wherein the inverse agonist has
a functional efficacy at the α_5 receptor subtype of less than 20%, and a
functional efficacy at the α_1 , α_2 and α_3 receptor subtypes of between -20
10 and +20 %.
3. A combination according to claim 1 or 2 wherein the inverse agonist
has a binding ration of greater than 10:1 to GABA_A receptors containing
the α_5 receptor subtype compared to GABA_A receptors containing the α_1 , α_2
15 or α_3 subtypes.
4. A combination according to claim 1 wherein the inverse agonist is
3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methyloxy-1,2,4-
triazolo[3,4-a]phthalazine.
20
5. A combination according to any one of the preceding claims wherein
the nicotinic agonist is selected from nicotine, lobeline,
tetramethylammonium, 1,1-dimethyl-4-phenylpyrazinium and ABT 418.
- 25 6. A pharmaceutical composition comprising a combination as defined
if any one of claims 1 to 5 and a pharmaceutically acceptable carrier for
simultaneous administration.
7. A kit of parts comprising a first pharmaceutical composition
30 comprising an nicotinic agonist and a first pharmaceutically acceptable
carrier and a second pharmaceutical composition comprising an inverse

agonist of the GABA_A α_5 receptor subtype and a second pharmaceutically acceptable carrier for simultaneous, separate or sequential administration.

8. A method of treatment of a subject suffering from a
5 neurodegenerative disorder or a cognitive deficit comprising administering to that subject a therapeutically effective amount of a combination of an nicotinic agonist and an inverse agonist of the GABA_A α_5 receptor subtype.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00800

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/50 A61K31/495 A61K31/465 A61K31/445 A61K31/42
A61K31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 04560 A (MERCK SHARP & DOHME ;REEVE AUSTIN JOHN (GB); STERNFIELD FRANCINE () 5 February 1998 (1998-02-05) abstract; claim 8 ---	1-8
A	WO 96 25948 A (MERCK SHARP & DOHME ;DAWSON GERARD RAPHAEL (GB)) 29 August 1996 (1996-08-29) cited in the application abstract; claims ---	1-8
A	EP 0 377 520 A (ELAN CORP PLC) 11 July 1990 (1990-07-11) claims ---	1-8
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

24 August 1999

Date of mailing of the international search report

31/08/1999

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00800

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ROSENBERG D R ET AL: "COGNITIVE ENHANCING AGENTS FOR THE TREATMENT OF SENILE DEMENTIA OF THE ALZHEIMER'S TYPE" DRUGS OF TODAY / MEDICAMENTOS DE ACTUALIDAD, vol. 26, no. 7, 1 October 1990 (1990-10-01), pages 449-471, XP000616601 ISSN: 0025-7656 page 459, paragraph 4</p> <p>-----</p>	1-8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 00800

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible combinations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those compounds explicitly mentioned in the claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/00800

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9804560 A	05-02-1998	AU 3551997 A	20-02-1998
		AU 3553997 A	20-02-1998
		EP 0915877 A	19-05-1999
		EP 0915875 A	19-05-1999
		WO 9804559 A	05-02-1998
		NO 990304 A	25-03-1999
		ZA 9706591 A	18-08-1998
WO 9625948 A	29-08-1996	AU 706515 B	17-06-1999
		AU 4725796 A	11-09-1996
		CA 2212058 A	29-08-1996
		EP 0810879 A	10-12-1997
		JP 11501302 T	02-02-1999
EP 0377520 A	11-07-1990	IE 62662 B	22-02-1995
		AT 111733 T	15-10-1994
		DE 69012591 D	27-10-1994
		DE 69012591 T	20-04-1995
		DK 377520 T	17-10-1994
		ES 2060941 T	01-12-1994
		JP 2225414 A	07-09-1990
		US 5069904 A	03-12-1991